REMARKS

Claim Status

Applicants have amended claims 1 and 24. Claims 2, 4, 8, 13-19, and 21 were cancelled by earlier amendment. Upon entry of this amendment claims 1, 3, 5-7, 9-12, 20, and 22-24 are pending in this application. Claims 1, 3, 5, 6, 11, 12, 20, and 22-24 are under examination and claims 7, 9, and 10 are withdrawn.

Support for the amendments to claims 1 and 24 can be found throughout the application as filed, including, page 6, line 25 and page 7 lines 6-10. Accordingly, these amendments do not add new matter and Applicants respectfully request their entry.

I) Maintained rejections

A) Enablement

Claims 20 and 22 remain rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled. Office Action at 3. The Examiner contends that "it is unclear how empirically testing of prospective embodiments...do [sic] no constitute undue experimentation." *Id.* at 5. The Examiner acknowledges that Applicants have demonstrated that lysates of the cells of the invention can raise an immune response to MUC1, TF, and glycophorin, in an *in vivo* model of the human immune system, but contends that it is unclear how this response would constitute an effective immune response against lymphoma, or which type of lymphoma would be suitable for treatment by Applicants' methods, and that the application does not describe *ex vivo* methods of treating a subject with a condition characterized by lymphoma . *Id.* at 5-7. The Examiner appears to predicate these concerns on a general allegation of unpredictability in the art for treating cancer, citing to Carbone *et al.*, *Seminars Cancer*

Biol. 14:399-405 (2004)(*Carbone*). *Id.* at 6-7. Finally, the Examiner alleges that knowledge in the art regarding treatment of advanced breast cancer with enzymatically desialylated glycophorin, which carried high densities of TF, is not predictive of success in treating lymphoma, based on the alleged differences in etiology and therapeutic end points of these diseases. *Id.* at 7.

Applicants traverse and respectfully submit that the Examiner has still failed to meet the Office's initial burden to adequately support a *prima facie* enablement rejection with specific technical reasoning. *See* M.P.E.P. §§ 2164.01 and 2164.04. For example, the Examiner's allegation that "it is unclear how empirically testing of prospective embodiments...do [sic] no constitute undue experimentation" is entirely conclusory and improperly places a burden on Applicants to argue why their presumptively enabled claims are in fact enabled. The remainder of the rejection does not discuss, or support the conclusion, that *undue* experimentation would be needed to practice Applicants' methods, which is the proper legal standard for determining compliance with the enablement requirement. *See* M.P.E.P. § 2164.01. Furthermore, Applicants reiterate that only "a *reasonable* correlation between the activity in question and the asserted utility" is needed. M.P.E.P. § 2107.03(I); *see also* M.P.E.P. § 2164.02 ("the [E]xaminer must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example [in an enablement rejection]").

Applicants discussed the individual *Wands* factors raised by the Examiner in the last Response (*see* pages 11-19, in particular) and will not address them further here, except to address the Examiner's general allegation of unpredictability in treating cancer. The only technical support for this allegation is *Carbone*. *See* Office Action at

7. As discussed in the last response, however, *Carbone* does not support a general allegation that treating cancer is unpredictable, but is simply a review article discussing the identification and classification of carcinogens. In a single, brief passage, *Carbone* merely reiterates the potential problem of treating cancers by a *single-target* approach, because of genetic heterogeneity in cancer. *See Carbone* at 400, left column, bridging first paragraph. The claimed methods, however, avoid this problem by using cells that express several pan-carcinomic markers. Thus, *Carbone* does not provide adequate grounds to question the enablement of Applicants claims.

Furthermore, knowledge in the art supports Applicants' position that the skilled artisan would believe that there is a *reasonable* correlation between generating an immune response to MUC1, TF, and glycophorin and treating lymphoma. For example, immunotherapy is a recognized strategy for treating cancer in general, while, e.g., TF and MUC1 have been recognized as useful antigens in particular. *See, e.g.*, specification at 1-2; *see also* Goletz *et al.*, *Advances Expt. Med. Biol.*, 535:147-62 (2003) at 156-159, of record (describing using TF in a variety of immunotherapies); Ichiyama, *Kareiigaku Kenkyusho Zasshi* 51(3,4): 93-110 (2000)(*Ichiyama*) at 110 (suggesting that MUC1-transformed K562-derived cells are useful for generating an immune response to cancer cells); Czuczman *et al.*, *J. Clin. Oncol.* 17:268-76 (1999), of record (using CD20 antibodies to treat lymphoma); and Brossart *et al.*, *Cancer Research* 61:6846-50 (2001) at abstract and introduction; attached (describing MUC1 expression in a variety of lymphomas). Thus, based on the art-recognized approach of treating cancer by immunotherapy, including using TF, MUC1, and glycophorin as effective antigens, and knowledge that at least MUC1 is expressed in a variety of

lymphomas, the skilled artisan would expect the claimed methods of treatment to reasonably correlate with Applicants' teaching that lysates of the cells of the invention can generate an *in vivo* immune response to TF, MUC1, and glycophorin.

In sum, Applicants aver that the Examiner has not adequately supported the present rejection, while the evidence as a whole supports the conclusion that no undue experimentation is needed to practice the claimed methods. Accordingly, Applicants respectfully request withdrawal of the rejection and reconsideration of the claims.

B) Novelty

Claim 1 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Ichiyama, *Kareiigaku Kenkyusho Zasshi* 51(3,4): 93-110 (2000)(*Ichiyama*), as evidenced by Benoist et al., *Immunol. Lett.* 34:45-56 (1992)(*Benoist*), and Karsten et al., *Cancer Res.* 58:2541-49 (1998)(*Karsten*). The Examiner appears to believe that TF is necessarily present in the MUC-1-transformed K562-derived cells of *Ichiyama*, although she acknowledges that it cannot be detected due to the presence of terminal sialic acids. Office Action at 8-9. Thus, the Examiner seems to believe that any carbohydrate structure that contains a core-1 unit "expresses TF."

Applicants disagree. As disclosed on page 6 of the specification, TF corresponds to *exposed* core-1 (Gal1-3GalNAc). *See* Specification at page 6, line 10. That is, Thomsen-Friedenreich antigen (TF) corresponds to core-1 without additional carbohydrates, such as terminal sialic acids and not more complex carbohydrate structures that contains core-1. Since the Examiner acknowledges that K562 cells, such as those described in *Ichiyama*, express only core-1-containing structures that also contain additional sialic acid structures, there should be no question that

Ichiyama—as evidenced by *Benoist and Karsten*—does not teach a cell that expresses TF on its surface. Again, Applicants' report that TF can only be detected in K562 cells after enzymatic cleavage of the sialic acid structures with neuraminidase underscores that these cells do not *express* TF. *See, e.g.,* Figures 2 and 3 and Table 2 in the application. Accordingly, *Ichiyama* does not teach all elements of Applicants' claim and does not anticipate it. This rejection should be withdrawn.

C) Obviousness

Claims 1, 5, 6, 11, 12, and 24 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over *Ichiyama*, as evidenced by Hinoda *et al.* (*J. Clin. Lab. Anal.* 7: 100-04 (1993), abstract) (*Hinoda*), in view of *Benoist* and *Karsten*, and further in view of U.S. Patent No. 7,268,120 by Horton, *et al.* (*Horton*). Office Action at 9. Again, the Examiner's rejection is based on the mistaken allegation that TF is necessarily present in certain complex core-1-containing carbohydrate structures. *Id.* at 10-11 (alleging that TF is "implicitly" comprised in the MUC1 DTR motif and that "Applicants have not provided evidence that MUC1 does not comprise the mucin-type O-glycan core 1, TF"). The Examiner also dismisses Applicants' report of unexpected and beneficial results (IgG response elicited by lysates of the cells of the invention) as an inherent property of the cells. *Id.* at 11.

This rejection should be withdrawn for at least the reason that *Ichiyama*, either alone or in combination with *Hinoda, Benoist, Karsten, and Horton*, fails to teach or suggest cells that express TF antigen on the cell surface. As discussed under the previous heading, TF antigen corresponds to an *exposed* core-1 structure, without additional terminal carbohydrate moieties. The only discussion of TF antigen in the

collective disclosure of the cited references is **1)** *Karsten's* report of *synthetic*, cell-free MUC1-derived peptides engineered to contain TF and **2)** *Horton's* erroneous suggestion that TF is an immunogenic polypeptide. These reports, however, in no way teach or suggest a cell line that expresses TF, MUC1, and glycophorin on its cell surface. *Horton's* mere recitation of the term TF is without probative value—a characterization unrebutted by the Office. *See also* page 20 of the last Response. *Karsten's* report of synthetic TF-containing peptides offers no teaching or suggestion of a cell line that expresses TF on its surface, which requires the cell's own synthesis machinery to produce the antigen. *See also* pages 21-22 of the last Response. Applicants have amended the claims to recite that the cells must *synthesize and express* MUC1, TF, and glycophorin to make this feature more clear. Thus, *Ichiyama*, either alone or in combination with *Hinoda, Benoist, Karsten, and Horton*, does not render Applicants' claims obvious.

Finally, Applicants address the Examiner 's allegation that the unexpected and beneficial results described in the Examples (e.g., the ability of cell lysates to elicit an immune response, including an IgG response) is merely an inherent property of the cells. Applicants submit that the K562-derived cells of *Ichiyama* would not exhibit this supposedly inherent feature since, as the Examiner has acknowledged, the core-1 motif in K562 cells is obscured by terminal sialic acids and is therefore unable to elicit an immune response. Accordingly, these cells would not be able to generate an immune response to TF, let alone the surprising and desirable IgG response. *See, e.g.*, Specification at 24, lines 4-10 and Example 4B-1 at 55.

Applicants request that this rejection be withdrawn.

II) New Objections and Rejections

A) Claim Objection

The amendment of claim 24 obviates the Examiner's objection.

B) Information Disclosure Statement

The Examiner indicated that three references submitted in the Information Disclosure Statement filed with the last Response —W. Paul *Fundamental Immunology* pp1007-09; M. Leffell *Human Immunology Handbook* pp1-45; and Snippe at al. *Vaccine Design* pp155-66—have been considered, but were lined-through on the returned SB-08 form because they did not include publication dates. Office Action at 12. With this Response, Applicants submit an SB-08 form listing these three references, including their publication dates, in full compliance with 37 C.F.R § 1.98. Applicants believe that this submission is timely and requires no additional fees or submissions. *See* M.P.E.P. § 609.04(IV).

C) Written Description/ New Matter

Claim 3 stands rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate written description for part "c" of the claim, which recites "subclones of (a) [F9] or (b) [D4] which express on the cell surface TF, MUC1, and glycophorin." Office Action at 12-13. The Examiner alleges that there is no structure/function relationship taught for the uncharacterized subclones of NM- F9 or NM-D4 expressing TF, MUC1, and glycophorin on the cell surface. *Id.* at 15-16.

Applicants traverse. The M.P.E.P. states that the fundamental factual inquiry for determining compliance with the written description requirement is "whether the specification conveys with reasonable clarity to those skilled in the art that, as of the

filing date sought, applicant was in possession of the invention as now claimed." M.P.E.P. § 2163.02. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting," or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *Id.*

In view of the plain meaning of the term "subclones" in the art, the description of subclones of F9 and D4 on pages 7-8 of the specification as filed, and Applicants' teachings on isolating and characterizing the F9 and D4 clones from mutagenized K562 cells, the skilled artisan would conclude that Applicants were in possession of subclones of F9 and D4 that express on the cell surface TF, MUC1, and glycophorin. For example, the specification explains that "subclones" of F9 and D4 cells are "cells or cells of a cell line which are derived from NM-F9 or NM-D4 and which occur due to naturally occurring alterations, e.g., mutations, but having similar characteristics." Specification at 7, lines 30-32. There is no question that Applicants were in possession of the F9 and D4 cell lines and that these cells express TF, MUC1, and glycophorin. The skilled artisan would certainly recognize that Applicants were in possession of cells or cell lines derived from F9 and D4, since methods of subcloning are routine in the art. Thus, the only question is whether Applicants were in possession of subclones F9 and D4 that *maintain* expression of TF, MUC1, and glycophorin on their cell surface.

Based on Applicants' teachings, however, the skilled artisan would understand that Applicants could readily test particular subclones to identify those that maintain expression of these antigens. Indeed, the selection—and subsequent characterization—of the F9 and D4 clones from mutagenized K562 cells described in

the application clearly illustrates this methodology. *See*, for example, Examples 2 (A2) and (A3)(describing selection of mutagenized K562 cells for TF and MUC1 expression, respectively) and Examples 3 (B-1-3)(characterizing the expression of various tumor antigens in F9 and D4 cells). Thus, not only have Applicants described sufficient "distinguishing identifying characteristics" of the claimed subclones, *e.g.,* expression of TF, MUC1, and glycophorin, which are readily assayable, but have also provided detailed protocols for how to select for maintaining the expression of these antigens. Accordingly, the skilled artisan would conclude that Applicants were in possession of the claimed subclones of F9 and D4 that express TF, MUC1, and glycophorin on their cell surfaces. Applicants courteously solicit the withdrawal of this rejection.

D) Nonobviousness

Claims 1 and 23 are newly rejected under 35 U.S.C. § 103(a) as allegedly obvious over *Ichiyama* in view of *Benoist*, *Karsten*, and further in view of Springer *J. Mol. Med.* 75: 594-602 (1997) (*Springer*). Office Action at 16-17. In addition to arguing that TF is inherently present (in a more complicated structure) in MUC1 DTR repeats, the Examiner alleges that, in view of *Springer*, it would be obvious to enzymatically desialate the glycophorin on the K562-derived cells of *Ichiyama* to obtain cells that have asialoglycophorin, which would supposedly meet the limitation of the claim 24. *Id.* at 17-18.

Applicants traverse. As previously discussed, the collective disclosures of *Ichiyama*, *Benoist*, and *Karsten* fail to teach or suggest cells that express TF, *i.e.*, exposed core-1. *Springer's* report of enzymatically disiasylating glycophorin in preparations of red blood cells does not remedy these teachings. In particular, a cell

enzymatically treated to remove sialic acid moities does not *express* TF or asialoglycophorin, since, as is known in the art, expression relies on the cell's own synthesis machinery. To further emphasize this feature, Applicants amended the claims to recite that the cells *synthesize and express* the recited antigens.

Advantageously, as discussed on page 6 of the application, cell lines that synthesize and express these antigens allow the skilled artisan to avoid **1)** using blood samples as a source of antigen expressing cells (instead, the cells of the invention can serve as a controlled source) and **2)** the need for enzymatic treatment to expose asialoglycophorin. Neuraminidase treatment would not be suitable for pharmaceutical application due to increased cost and difficulty of production. Moreover, enzymatic treatment of live cells will only result in a transient display of asialoglycophorin, since the synthesis of surface proteins is generally ongoing and newly-produced surface antigens will again carry sialic acid, which will obscure the core-1 motif.

Accordingly, *Ichiyama*, *Benoist*, *Karsten,* and *Springer*—alone or in combination—do not teach or suggest the claimed cell lines and do not render them obvious. Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing the pending claims in condition for allowance. Applicants submit that the proposed amendments of claims 1 and 24 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier

claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Furthermore, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims. Finally, the Examiner is encouraged to call the undersigned with any questions or comments.

Applicants do not believe any fees are required to enter this amendment. However, in the event of an error, the Commissioner is authorized to charge any required fees to deposit account number 06-0916.

Respectfully submitted,

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Dated: September 23, 2009

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Attachments:

PTO/SB/08 form listing previously submitted references considered by the Examiner

Brossart et al., *Cancer Research* 61:6846-50 (2001)

ATTACHMENT 1